

Gluten tolerance; potential challenges in treatment strategies

Justine Bold¹, Kamran Rostami^{1,2}

¹*Institute of Health, Social Care and Psychology University of Worcester UK*

²*University Hospital Birmingham, UK*

ABSTRACT

Tolerable gluten thresholds in gluten free products have long been debated together with issues of cross contamination of gluten free cereals during the milling process. It is well established that a totally gluten free diet is virtually impossible owing to the presence of traces of gluten. It is estimated that daily consumption of gluten from contaminated gluten free foods is in the range of 5 to 50 mg. We believe evidence is mounting that it may be possible for some coeliac patients to tolerate gluten above the limits considered permissible at threshold levels. Conversely, it seems there is evidence that some patients might have a much lower threshold for gluten. Whatever would be the individual threshold, GFD may be of benefit to any symptomatic patients even those with milder enteropathy like microscopic enteritis.

Keywords: Gluten tolerance, Coeliac disease, Gluten free diet.

(Please cite as: **Bold J, Rostami K. Gluten tolerance; potential challenges in treatment strategies. Gastroenterology and Hepatology From Bed to Bench 2011;4(2):53-57.**)

Our understanding of coeliac disease (CD) diagnosis, pathogenesis and therapy has significantly improved over the last two decades. A gluten free diet (GFD) is considered an effective therapy in most symptomatic coeliac patients (1). Dietary management is also essential in the treatment of complications like osteoporosis, anaemia and associated disorders like lactose intolerance and type I Diabetes. However, most patients with CD can tolerate small amounts of gluten in their diet (2). The highest safest level is debated and presumably differs between individuals. Therefore, the appropriateness of a life-long GFD for a some of coeliac patients is now under discussion (1, 3, 4).

The study by Errichiello et al, (5) evaluates compliance to a gluten-free diet (GFD) and

explores the relationship of diet with well-being. This study has some interesting findings, suggesting that moderate amounts of gluten may be tolerated by some coeliac patients without ill effects. The study of 204 young coeliac patients in Italy, reports that 54/204 (26.5%) patients transgressed from the GFD. Of the 54 poor compliers, 14 (25.9%) were consuming 1-5 grams gluten/day and 11 (20.4%) reported consuming more than 5 grams/day. Five grams gluten/day is approximately half of the intake that might be expected in a normal diet – where gluten intake averages at 10-20 grams/day (6). Errichiello et al. report that 31/54 (57.4%) of the poor compliers were asymptomatic and that a large proportion 39/54 (73.6%) of poor compliers had negative tTG and only 14/54 (26.4%) had a positive tTG. Biopsies and histological testing were not undertaken.

Given that 54% of those in the study reported some limitation in their social lives, one has to

Received: 5 March 2011 Accepted: 15 March 2011

Reprint or Correspondence: Kamran Rostami, MD, PhD. School of Clinical and Experimental Medicine, University of Birmingham, UK

E-mail: Kamran.rostami@nhs.net

question if it may be possible to find a way to predict individual tolerance to gluten among coeliac patients? It may be that some coeliac patients have a permanent tolerance to gluten at some level and that this can contribute to improved social integration and quality of life (3, 4). Perhaps a life-long GFD may not be necessary for every coeliac patient!?

Tolerable gluten thresholds in gluten free products have long been debated together with issues of cross contamination of gluten free cereals during the milling process. It is well established that a totally gluten free diet is virtually impossible owing to the presence of traces of gluten. It is estimated that daily consumption of gluten from contaminated gluten free foods is in the range of 5 to 50 mg (7). Permitted levels of gluten in gluten free foods vary in different areas of the globe. The Codex Alimentarius (World Health Organisation & UN Food and Agriculture Organization Commission) recommend \leq 200 parts per million (ppm) of gluten is permitted in foods considered to be free of gluten (7). An intake of gluten below 10 mg/day is generally considered safe for most coeliac patients and not thought likely to cause histological abnormalities (8). Moreover, several recent studies have demonstrated that oats (which contain gluten) can be tolerated by many coeliac patients (9, 10). The prolamine gliadin in wheat constitutes 40% of the cereal; the percentages are similar for rye and barley. However, in oats, avenins constitute only 15% of the cereal (11).

We believe evidence is mounting that it may be possible for some coeliac patients to tolerate gluten above the limits considered permissible at threshold levels. Conversely, it seems there is evidence that some patients might have a much lower threshold for gluten. A GFD may be of benefit to any symptomatic patients even those with milder enteropathy like microscopic (12-15). Under current guidelines a GFD is recommended to gluten sensitive cases with villous atrophy. This

policy excludes a range of symptomatic gluten sensitive cases with atypical presentation including those with small bowel Microscopic changes (Marsh 0-II). It is well known that patients with microscopic enteritis (Marsh 0-II) may also develop gluten related antibodies and minor mucosal lesions may not be apparent during routine histological analysis (16). Their appearance may precede, by months or years, the further histological progression of the disease (17, 18). The sub-microscopic changes might be due to unknown factors in CD immuno-histogenesis that lead to malabsorption syndrome much earlier than expected. It is, therefore, clear that malabsorption may occur even in patients with sub-microscopic mucosal abnormalities (12-14). This evidence would support implementing a GFD in symptomatic cases, which feature malabsorption even at microscopic stage with the absence of villous atrophy.

When presentation is atypical, it can be a challenge to identify a patient where a GFD may be of benefit. Similarly, identification of the subgroups that may need less restriction with their gluten intake could also be extremely difficult (Figure 1). There are coeliac patients for whom gluten would be detrimental, as studies show histological abnormalities with moderate (200-1000mg/day) intakes (19). There is also overwhelming evidence that a GFD might be beneficial in coeliac patients presenting with microscopic lesions (15, 20, 21). In an ideal world our aim should be to identify cases with different tolerance for gluten based on future accurate tests as gluten tolerance might be variable between different individuals (5). Hopefully by developing sensitive marker in future we may achieve the goal to lessening the degree of gluten restriction in suitable candidate and improve the quality of life in those patients with a higher threshold for gluten toxicity.

Previous studies (3, 4) and the study performed by Errichiello et al. show that some patients would

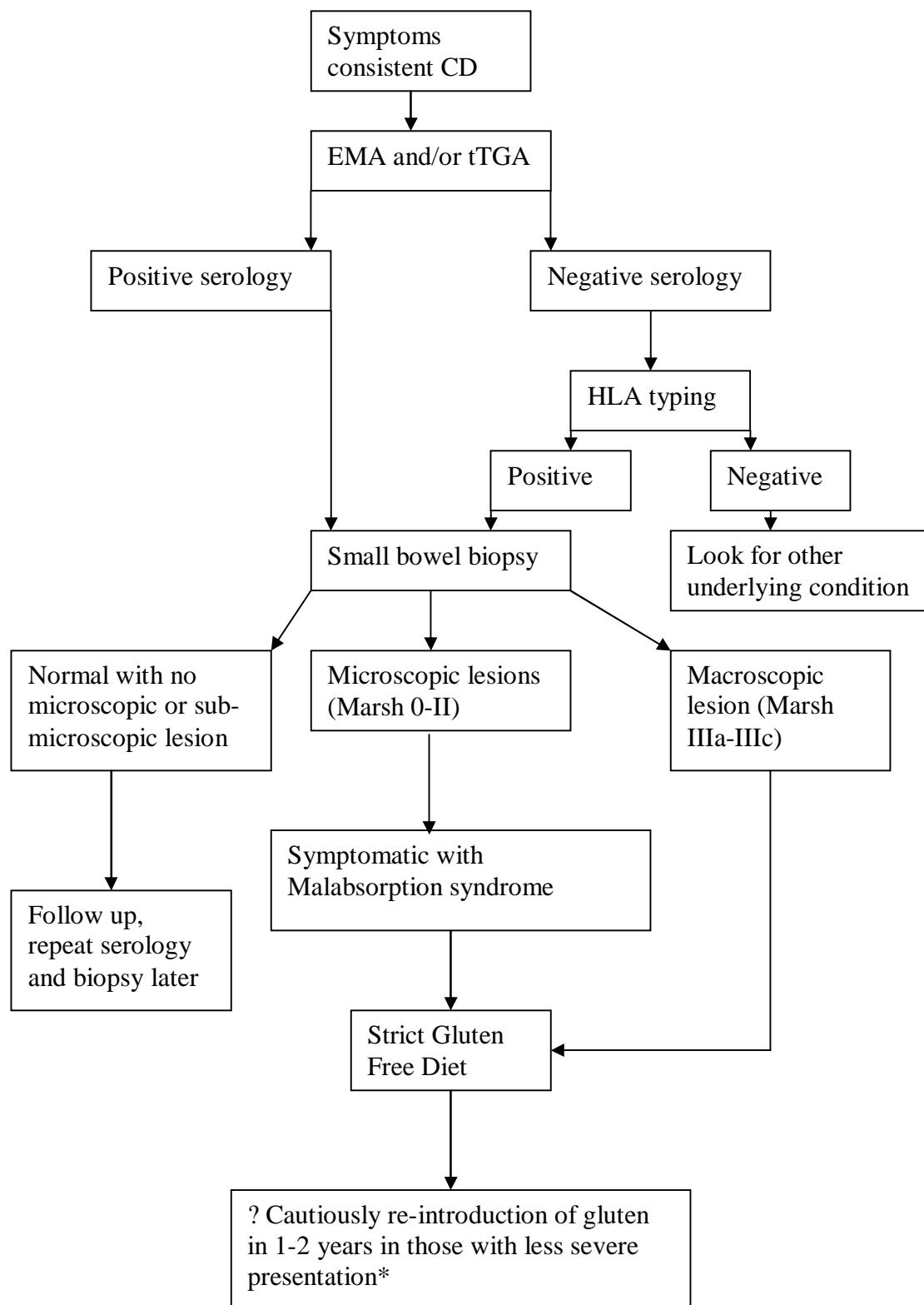


Figure 1. Gluten free diet guide. * The subgroup with a potential higher

tolerate even more than 5g gluten/day and still remain symptom free with negative serology.

Unfortunately, antibody screening is not the most sensitive test for assessing intestinal mucosal

recovery due to their poor correlation with histological damage (22). The antibodies are mostly associated with severe lesions and macroscopic mucosal damage like (sub)-total villous atrophy (22, 23).

Undoubtedly, the future challenge is to sharpen the criteria in order to balance the amount of gluten restriction and gluten intake as well as qualifying the atypical subgroup where a GFD would also be appropriate. Further large-scale studies would be required to characterise the individuals with higher and lower thresholds for gluten toxicity. If a sensitive algorithm was validated in future studies, it could predict tolerance to gluten through analysis of the indicative parameters.

References

1. Troncone R, Auricchio R, Granata V. Issues related to gluten-free diet in coeliac disease. *Curr Opin Clin Nutr Metab Care* 2008; 1: 329-33.

2. Ciclitira PJ, Ellis HJ, Lundin KE. Gluten-free diet - what is toxic? *Best Pract Res Clin Gastroenterol* 2005; 19: 359-71.

3. Hopman EG, von Blomberg ME, Batstra MR, Morreau H, Dekker FW, Koning F, et al. Gluten tolerance in adult patients with celiac disease 20 years after diagnosis? *Eur J Gastroenterol Hepatol* 2008; 20: 423-29.

4. Matysiak-Budnik T, Malamut G, de Serre NP, Grosdidier E, Seguier S, Brousse N, et al. Long-term follow-up of 61 coeliac patients diagnosed in childhood: evolution toward latency is possible on a normal diet. *Gut* 2007; 56: 1379-86.

5. Errichiello S, Esposito O, Di Mase R, Camarca ME, Natale C, Limongelli MG, et al. Celiac disease: predictors of compliance with a gluten-free diet in adolescents and young adults. *J Pediatr Gastroenterol Nutr* 2010; 50: 54-60.

6. van Overbeek FM, Uil-Dieterman IG, Mol IW, Kohler-Brands L, Heymans HS, Mulder CJ. The daily gluten intake in relatives of patients with coeliac disease compared with that of the general Dutch population. *Eur J Gastroenterol Hepatol* 1997; 9: 1097-99.

7. Catassi C, Fabiani E, Iacono G, D'Agate C, Francavilla R, Biagi F, et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. *Am J Clin Nutr* 2007; 85: 160-66.

8. Akobeng AK, Thomas AG. Systematic review: tolerable amount of gluten for people with coeliac disease. *Aliment Pharmacol Ther* 2008; 27: 1044-52.

9. Holm K, Maki M, Vuolteenaho N, Mustalahti K, Ashorn M, Ruuska T, et al. Oats in the treatment of childhood coeliac disease: a 2-year controlled trial and a long-term clinical follow-up study. *Aliment Pharmacol Ther* 2006; 23: 1463-72.

10. Ellis HJ, Ciclitira PJ. Should coeliac sufferers be allowed their oats? *Eur J Gastroenterol Hepatol* 2008; 20: 492-93.

11. Janatuinen EK, Pikkarainen PH, Kemppainen TA, Kosma VM, Jarvinen RM, Uusitupa MI, et al. A comparison of diets with and without oats in adults with celiac disease. *N Engl J Med* 1995; 333: 1033-37.

12. Sbarbati A, Valletta E, Bertini M, Cipolli M, Morroni M, Pinelli L, et al. Gluten sensitivity and 'normal' histology: is the intestinal mucosa really normal? *Dig Liver Dis* 2003; 35: 768-73.

13. Maki M, Holm K, Collin P, Savilahti E. Increase in gamma/delta T cell receptor bearing lymphocytes in normal small bowel mucosa in latent coeliac disease. *Gut* 1991; 32: 1412-14.

14. Paparo F, Petrone E, Tosco A, Maglio M, Borrelli M, Salvati VM, et al. Clinical, HLA, and small bowel immunohistochemical features of children with positive serum antiendomysium antibodies and architecturally normal small intestinal mucosa. *Am J Gastroenterol* 2005; 100: 2294-98.

15. Rostami KV, Villanacci V. Microscopic enteritis: novel prospect in coeliac disease clinical and immunohistogenesis. Evolution in diagnostic and treatment strategies. *Dig Liver Dis* 2009; 41: 245-52.

16. Mohamed BM, Feighery C, Coates C, O'Shea U, Delaney D, O'Briain S, et al. The absence of a mucosal lesion on standard histological examination does not exclude diagnosis of celiac disease. *Dig Dis Sci* 2008; 53: 52-61.

17. Troncone R, Greco L, Mayer M, Paparo F, Caputo N, Micillo M, et al. Latent and potential coeliac disease. *Acta Paediatr Suppl* 1996; 412: 10-14.

18. Collin P, Helin H, Maki M, Hallstrom O, Karvonen AL. Follow-up of patients positive in reticulin and gliadin antibody tests with normal small-bowel biopsy findings. *Scand J Gastroenterol* 1993; 28: 595-98.

19. Catassi C, Rossini M, Ratsch IM, Bearzi I, Santinelli A, Castagnani R, et al. Dose dependent

effects of protracted ingestion of small amounts of gliadin in coeliac disease children: a clinical and jejunal morphometric study. *Gut* 1993; 34: 1515-19.

20. Kaukinen K, Maki M, Partanen J, Sievanen H, Collin P. Celiac disease without villous atrophy: revision of criteria called for. *Dig Dis Sci* 2001; 46: 879-87.

21. Tursi A, Brandimarte G. The symptomatic and histologic response to a gluten-free diet in patients with borderline enteropathy. *J Clin Gastroenterol* 2003; 36: 13-17.

22. Rostami K, Kerckhaert JP, Tiemessen R, Meijer JW, Mulder CJ. The relationship between anti-endomysium antibodies and villous atrophy in coeliac disease using both monkey and human substrate. *Eur J Gastroenterol Hepatol* 1999; 11: 439-42.

23. Dickey W, Hughes D. Disappointing sensitivity of endoscopic markers for villous atrophy in a high-risk population: implications for celiac disease diagnosis during routine endoscopy. *Am J Gastroenterol* 2001; 96: 2126-28.